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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/599,594 | 06/22/2000 | Irina Nazarenko | 0942.4980002/RWE/SEZ | 8750 |

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1655 | 17 |

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/599,594 | Nazarenko et al |
| **Examiner** | **Art Unit** |
| Jeffrey Fredman | 1655 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Nov 28, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *10-22, 47, and 56-67* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-22, 47, and 56-67* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

## DETAILED ACTION

### *Information Disclosure Statement*

1. The information disclosure statement filed January 12, 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

### *Claim Objections*

2. Claims 10-22 and 47 are objected to because of the following informalities: The claims include limitations from nonelected claims. Appropriate correction is required.

### *Claim Rejections - 35 USC § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10-16, 18, 20-22, 47, 56-58, 60-62, and 65-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Heller (U.S. Patent 5,565,322).

Heller teaches a method for the detection of a target nucleic acid molecule in a sample (abstract and column 4) comprising:

hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see figures 2A, 2B, 3A, 3B and column 23, lines 15-29 for examples of oligonucleotides with detectable labels located internally which are also near the 3' or 5' termini) and said one ore more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see column 25, lines 62-66, where Heller shows that there is no energy transfer at 90 C, when there is no double stranded molecules but that upon cooling and rehybridization to reform the double stranded energy transfer system, there is a change in observable properties in that energy transfer is restored), and

detecting the presence or absence of one or more target nucleic acid molecules (column 17, line 45 to column 19, line 56) which may include a PCR amplification step thereby incubating the nucleic acid mixture to synthesize additional nucleic acid (see column 21, lines 32-35).

Heller teaches the use of Fluorescein and Rhodamine (see Table 2 and column 11).

Heller teaches the location of the acceptor fluorophore within 20 nucleotides of the 3' end (see column 23, line 15). Heller also shows the use of fluorescein, a detectable label, on column 26, line 24, which is 6 nucleotides from the 3' termini.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al in view of Weimar et al (U.S. Patent 6,248,526).

Nazarenko teaches a method for the quantifiaction or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of

synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

Nazarenko does not teach the use of a TAMRA label in the place of the DABCYl label such that the label will be a fluorphore which will undergo a detectable change.

Weimar teaches the use of TAMRA labels as equivalent quencher molecules to DABCYL and TAMRA labels will undergo a detectable observable change (column 4, lines 25-31).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Nazarenko method of detection with the use of an equivalent TAMRA label because Weimer expressly teaches the equivalence of the TAMRA and DABCYL labels. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Here, the equivalency is recognized in the Weimer prior art reference.

With regard to the exact positioning of the bases near the 3' end, since Weimar expressly teaches such positioning, the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions

> of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

7. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller in view of Nazarenko et al.

Heller teaches a method for the detection of a target nucleic acid molecule in a sample (abstract and column 4) comprising:

hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see figures 2A, 2B, 3A, 3B and column 23, lines 15-29 for examples of oligonucleotides with detectable labels located internally which are also near the 3' or 5' termini) and said one ore more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see column 25, lines 62-66, where Heller shows that there is no energy transfer at 90 C, when there is no double stranded molecules but that upon cooling and rehybridization to reform the double stranded energy transfer system, there is a change in observable properties in that energy transfer is restored), and

detecting the presence or absence of one or more target nucleic acid molecules (column 17, line 45 to column 19, line 56) which may include a PCR amplification step thereby incubating the nucleic acid mixture to synthesize additional nucleic acid (see column 21, lines 32-35).

Heller teaches the use of Fluorescein and Rhodamine (see Table 2 and column 11).

Heller teaches the location of the acceptor fluorophore within 20 nucleotides of the 3' end (see column 23, line 15). Heller also shows the use of fluorescein, a detectable label, on column 26, line 24, which is 6 nucleotides from the 3' termini.

Heller does not teach the use of hairpin primers in the PCR reaction, nor does Heller teach placement of the fluorophores either four or five nucleotides from the 3' terminus.

Nazarenko teaches a method for the quantifiaction or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Heller detection method using PCR with a hairpin primer as taught in the Nazarenko method since Heller states "A multiple donor system comprised of

such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications (column 10, lines 23-27)". Thus, an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce background to as low a level as possible. Nazarenko provides motivation to combine with Heller, stating that "The main advantage of this method is the generation of the fluorescent signal by the product itself, rather than by the hybridized probe, as in previous methods. This keeps background low and allows real-time quantification of the amplified DNA over an extremely wide dynamic range (page 2521, column 1)".

Thus, an ordinary practitioner seeking to achieve a system with as minimal a background as possible for diagnostic uses in order to detect nucleic acids associated with diseases or infections would have been motivated to use the primer of Nazarenko because Nazarenko expressly states that this primer keeps background low as desired by Heller, who uses multiple fluorophores to relay energy transfer to also keep background low. An ordinary practitioner would have been motivated to form such a multiple relay system of Heller, combined into the hairpin primer of Nazarenko, in order to yield an even further reduced background, thereby further improving the sensitivity and low background of the resultant assay, making it more suitable for detection of nucleic acids for diagnostic purposes.

With regard to the exact positioning of the bases near the 3' end, since Heller expressly teaches such positioning, including six from the 3' end and 11 from the 3' end, the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

***Response to Arguments***

8. Applicant's arguments filed November 28, 2001 have been fully considered but they are not persuasive.

Applicant argues that Nazarenko does not disclose internal oligonucleotides and that the '526 patent does not teach the use of an oligonucleotide located internally. This is not correct for two reasons. First, the '526 patent expressly states regarding the TAMRA label that "In another preferred embodiment, a label or label system is attached to the primer at or ***near*** its 3' end and has an interactive label (column 2, lines 43-45 (emphasis mine))". This is an express statement by Weimer that the TAMRA label may be internal, ie not at the 3' end but simply ***near*** the 3' end. This teaches the use of an internal label. Second, since Nazarenko teaches the express use of an internal quencher molecule, DABCYL and an ordinary practitioner would have been motivated to

substitute an art recognized equivalent quencher molecule such as TAMRA for the DABCY quencher.

***Conclusion***

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

**Jeffrey Fredman**
**Primary Patent Examiner**
**Art Unit 1655**